A Model of Diffusion Weighted MRI in grey matter - a multiparametric approach using global solutions

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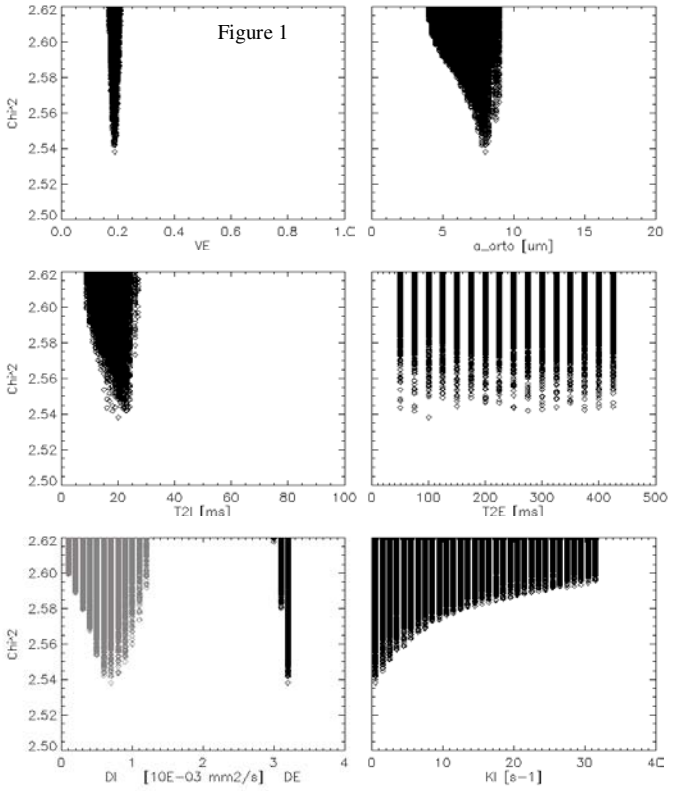
INTRODUCTION: Diffusion weighted imaging of water plays an important role in the detection of acute cerebral ischemia where a significant decrease of the apparent diffusion coefficient (ADC) is observed. The underlying cellular mechanisms responsible for this ADC change are still uncertain, as many factors contribute to the diffusion-weighted signal obtained from the cellular compartments. These factors include compartmental diffusion coefficients and transverse relaxation times as well as restriction and exchange effects caused by cell membranes. Therefore tissue water diffusion has been modeled analytically and numerically in a number of studies (1-3). These studies have produced realistic ADC reduction in the prediction of the cell swelling, but fail to produce realistic absolute values of ADC, cellular volume fractions and tortuosity. Most studies have assumed negligible influence of T2 relaxation effects and/or assumed slow or fast exchange. However, T2 may have a profound effect on the diffusion signal in cases of slow exchange (and long diffusion time - Δ) when compartmental T2 differences are large, the signal become excessively weighted towards the compartment with the longest T2 - which in turn means that the ADC will depend on the echo time. We hypothesize that absolute ADC values and volume fractions similar to that observed in experimental studies may be produced by including T2 relaxation and exchange in a model of normal gray matter as well as volume fractions, diffusion coefficients and intracellular restriction. To ensure global solutions, we tested the hypothesis in the following way: for all combinations of a wide range of values of all model parameters we compared the model output with experimental data obtained from grey matter in normal volunteers.

METHODS: The model consists of a prolate ellipsoid shaped intra-cellular compartment mimicking the neurons and glial cells in gray matter, as well as an extra-cellular compartment (V_E), as the majority of the intracellular volume consists of dendrites and processes having internal diameters of a few microns compared to a length an order of magnitude longer (4). We chose an analytical approach to describe the magnetization change (M_I, M_E) due to diffusion and exchange between several compartments based on the work of Kärger et al. 1988 (5) adding individual T_2 relaxation rates of all compartments:
$dM_I/dt = -(\gamma g\delta)^2\ ADC_I\ M_I - k_I\ M_I + k_E\ M_E - (1/T_{2I})\ M_I$, $dM_E/dt = -(\gamma g\delta)^2\ ADC_E\ M_E - k_E\ M_E + k_I\ M_I - (1/T_{2E})\ M_E$. The intra-cellular ADC_I was found using a one-dimensional model of restricted diffusion within infinite long parallel membranes with the separation a_{orto} (3,6) denoting the restriction length (short axis of the ellipsoid) and D_I the intracellular free diffusion coefficient. The extracellular apparent diffusion was found from $ADC_E = D_E/\lambda^2$ (7) where D_E denotes the extra cellular free diffusion and λ the extracellular torutosity. Taking the effect of TE into account in a PGSE experiment where TE>Δ, the equations are integrated in the interval: t=[0, Δ] to get the signal from the respective compartments, during application of the diffusion gradients and omitting the first term in the interval t=[Δ, TE] where there is no effect from the diffusion gradients, but still T_2 relaxation and exchange effects. Setting the term $(\gamma g\delta)^2 = b/\Delta$ we get the total signal: $S(b) = M_I(b) + M_E(b)$. The equations are solved for diffusion gradients both parallel and orthogonal to the ellipsoids long axis and angle averaged to model isotropic gray matter. Experimental data was obtained from five healthy volunteers using diffusion weighted PGSE EPI with b-factors 0 - 4500 s/mm2 and $\delta/\Delta/TE$=24/35/78 ms. The influence of echo time on the diffusion experiment was examined by the same diffusion weighted pulse sequence (δ/Δ = 17.3 ms/23.9 ms in order to have a low minimum TE) in a TE range from 54 to 175 ms, but due to the time limitations in experiments involving subjects, limited slew rate and gradient amplitude only for two b-values (0 and 1500 s/mm^2) so that an ADC_{1500} could be estimated. The extreme number of combinations (7.7E09) in this approach required considerable amount of computing capacity or time (approximately 6 months on a standard PC). Therefore we utilized a state-of-the-art sixteen CPU Linux PC-cluster and used the averaged diffusion weighted signal versus b-value data set for the five volunteers in order to have a realistic calculation time. All parameters and value permutations were used as input to the model and the chi-squared was used as a goodness of fit measure.



RESULTS: The best global solutions are shown in figure 1. There are distinct minima for V_E (ca. 0.19), D_I (ca. 0.7E-03 mm^2/s), T_{2I} (ca. 23 ms), restriction length (a_{orto}ca. 7 µm) or asymptotes for K_I ($\rightarrow$ 0 s^{-1}), D_E ($\rightarrow$3.2E-03 mm^2/s) except for the extra-cellular transverse relaxation T_{2E} where good solutions were found for a wide range (50-450 ms). The experimental ADC-TE data (figure 2) indicated a significant increase of the ADC as the echo time increases. Using the global minimas and asymptotes as well as the range of experimental echo times as input we get a match to the experimental ADC within the error of the experimental data (fig. 2).

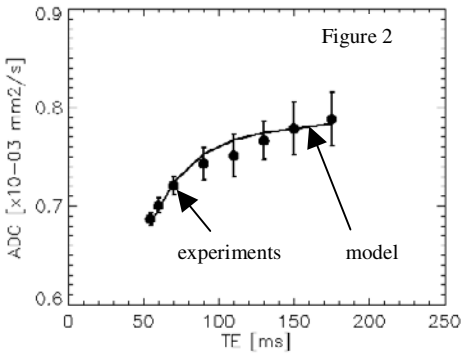


Figure 2: ADC-TE: Experimental data obtained at b=1500 s/mm2 and model output using the minimas and T_{2E} =275 ms, K_I = 5 s^{-1}

DISCUSSION: These results support the hypothesis that T_2 relaxation cannot be neglected in modelling water diffusion of brain tissue. The indications of slow exchange and the T_2 heterogeneity between compartments predict a dependence of the ADC on the echo time, which was also supported by the experimental data. The presented approach is judged feasible for further investigation of the underlying cellular mechanisms of tissue ischemia.

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